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Scientists Find a Switch that Renews Sperm-Producing Stem Cells

Researchers have discovered a master genetic switch that regulates the self-renewal of sperm-producing stem cells. Mice that were genetically engineered to lack the switch quickly exhausted their sperm-producing stem cells, rendering them incapable of producing sperm.

The researchers said their finding offers new opportunities for exploring how spermatogenesis is regulated in mammals.

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— **Kenneth M. Murphy**

A large research team led by Howard Hughes Medical Institute investigator Kenneth Murphy published their findings in the August 18, 2005, issue of the journal *Nature*.

Murphy and his colleagues at Washington University School of Medicine in St. Louis collaborated on the studies with researchers from University of Illinois at Urbana-Champaign, Genentech, Washington State University, University of Texas Southwestern Medical School, University of Basel, Friedrich Miescher Institute in Switzerland, McMaster University, Southern Illinois University School of Medicine and The University of Dayton.

In their studies, the researchers sought to understand the role of the switch, which is called ERM, in Sertoli cells. These cells form a critical supporting "niche" for spermatogonial stem cells. Niches are microenvironments that provide stem cells with physical support and other nurturing factors that aid in their proper development and functioning. Stem cells are immature precursor cells that divide to form daughter cells, one of which develops into a mature cell, while the other "self-renews" to maintain its identity as a stem cell capable of supporting further proliferation.

"While it was known that Sertoli cells are the niche cells in the seminiferous tubules, not a whole lot was known about their specific characteristics and the

signaling they provided,” said Murphy. It was not known that ERM—a member of a large family of transcription factors that control gene expression—played any role in controlling the stem cell niche, he said.

Murphy and his colleagues gained the first clue to ERM's function in spermatogenesis when they created mice lacking the gene for the transcription factor. Their original intent was to explore the effects of knocking out ERM on T cells of the immune system. “When we did the standard analysis of the effects of this ERM knockout, however, the most glaring phenotype was a very rapid sterility that arose in all the males,” said Murphy. “We decided it was an excellent research opportunity, so we took it.”

The scientists' physiological analysis of the mice revealed that the animals rapidly depleted the stem cells necessary for normal spermatogenesis. Using various tracers, the researchers determined that the gene for ERM is expressed in Sertoli cells, indicating that it likely plays a role in the spermatogonial stem cell niche.

The researchers performed microarray analysis on the testes of young mice to determine what genes were affected by the loss of ERM expression. Microarrays enable scientists to look at the relative activity of thousands of genes at once. This microarray analysis, which was undertaken before the total loss of seminiferous epithelium, revealed that knocking out ERM reduced expression of a small number of genes that were specifically expressed in spermatogonia—the earliest cell in spermatogenic differentiation.

“This was really exciting, because in otherwise normal-looking testes, we were seeing a decrease in factors known to be associated with the spermatogonial stem cells,” said Murphy. “While a lot is known about spermatogenesis, more was known about processes within the sperm cell itself, rather than the regulatory factors acting from the outside on the stem cell from the niche” he said. More detailed study of the seminiferous tubules of the knockout mice revealed that they were lacking stem cells even before the obvious depletion of sperm cells was detectable.

The researchers also performed microarray analysis to determine which genes in the Sertoli cells of the knockout mice were affected by the lack of ERM. The researchers determined that some of the genes switched off in the Sertoli cells of ERM-knockout mice are the same as those implicated in regulating the stem cell niche for the hematopoietic stem cell needed for blood formation, or hematopoiesis. “So this suggests that maybe the mechanism by which Sertoli cells maintain spermatogonial stem cell identity, is similar to the mechanisms in hematopoietic stem cells,” said Murphy.

Murphy said that the discovery of ERM is important because “as far as we know it represents the first transcriptional regulator of a vertebrate stem cell niche.” He said that further study of the genes that are targets of ERM control could yield new information about the largely unknown factors that regulate the production and development of spermatogonial stem cells.